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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,287	10/08/2003	G. Roger Askew	032796-179	5825

21839 7590 06/09/2005

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POST OFFICE BOX 1404
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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/680,287	**Applicant(s)** ASKEW ET AL.	
	Examiner Joanne Hama, Ph.D.	**Art Unit** 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2005*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *14-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/8/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date *1/16/04;7/22/04*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.05

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on March 9, 2005 is acknowledged. The traversal is on the ground(s) that

1) the restriction requirement is a discretionary tool for examiners and requires that burden be shown (Applicant's response, page 17, point 1),

2) based on the classification of the claims, which are drawn mostly to 800 or 536, that claims should be rejoined, and that a new restriction with species election of HBM, LRP5, or LRP6 be issued (Applicant's response, page 18, point 2)

3) HBM is a polymorphic variant of LRP5 and should be considered with LRP5. LRP6 is a member of the low density lipoprotein receptor-related protein family, which like LRP5 is involved in regulation of the Wnt pathway (Applicant's response, page 19, point 3).

This has been found persuasive in part.

With regards to the argument that the restriction requirement is a discretionary tool for examiners and require that burden be shown, the Examiner has pointed out that burden was demonstrated by the fact that each of the transgenic animals in Inventions I-V, or the animals used in methods (e.g. claim 21) were independent and distinct and will require separate and non-co-extensive search in the patent and non-patent literature. Despite the fact that the transgenic animals are under the classification 800, each animal is independent in distinct because of their recognized divergent subject matter and the search for one group is not required for the search of another group (see

Restriction Requirement, page 37, bottom). Being classified in the same class and subclass does not mean that all the transgenic animals are the same. Applicants are reminded that placing an invention in a class/subclass is not an indicator that they are not patentable distinct and that there is no search burden. The Examiner has also pointed out with regards to Inventions I-III are unique because each animal is comprised of a different transgene, of which, expression of each transgene will result in a distinct protein, which has a specific function in a cell. With regards to the knockout animals of Inventions IV-V, the knockout animals will have different phenotypes from each other because LRP5 is a gene that is distinct from LRP6. This separation of overexpression animals, knockout animal, and knockout-knockin animals also applies to the methods that use them. For example, claim 21 comprises overexpression animals (claim 21, sub a, sub i), knockout/knockin animals (claim 21, sub a, sub ii, first half of sub ii), knockout animals (claim 21, sub a, sub ii, second half of sub ii). These are distinctly different transgenic animals because a transgenic overexpression animal is an animal wherein the animal overproduces the gene product of interest. This is genetically and phenotypically different from a transgenic knockout animal, wherein the gene of interest has been disrupted. Searching a knockout animal will not yield arts that are relevant to a transgenic animal that overexpresses a protein. A transgenic knockout/knockin animal is distinct from an overexpression animal and a knockout animal because one gene of interest has been replaced with a second gene of interest. The knockout/knockin mouse is distinct from the knockout mouse because in addition to losing one gene of interest, a second gene of interest is being used to study the effects of the second gene on the animal. The knockout/knockin mouse is distinct from the overexpression mouse because the unlike the overexpression mouse, the knockout/knockin mouse is missing a gene of interest. Therefore, these transgenic animals are distinct. With regards to the transgenic animals in which LRP5 or LRP6 is otherwise disrupted or modulated (claim 21 sub a, sub iii), these animals can be hypermorphs (animals that overexpress a gene of interest, similar to the transgenic overexpression animals) or hypomorphs (animals that express the gene product of interest that is less than what is produced in the wild type). Both of these mice will be considered with the overexpression mice. Each of the transgenic animals (overexpression, knockout, and knockout/knockin) are comprised of different genetic modifications, of which different phenotypes will result from each of the different genetic modifications. As such, each transgenic animal, as a result of their genetic modifications, will be used independently and distinctly in each method.

With regards to the issue that HBM is a variant of LRP5, the Examiner considered the Applicant's argument and found it convincing. Because HBM and LRP5 will work in the same genetic pathway, the search involved in LRP5 and HBM will be coextensive and thus not a burden. For this reason, the analysis of a transgenic animal comprising an overexpression transgene of HBM has been combined with the analysis for a transgenic animal comprising an overexpression transgene of HBM. It is noted that claim 2, is encompassed by claim 1. Claim 2 is a transgenic animal comprising a transgene construct that overexpresses a sequence that encodes SEQ ID NO 4. SEQ ID NO. 4 is the protein sequence of HBM. Claim 2 has been included in this analysis.

Therefore, as the Examiner has reconsidered the Applicant's request to reconsider the Restriction Requirement, the new groupings of inventions are as follows:

I. (claims 1-13) A transgenic animal having somatic and/or germ cells comprising a nucleic acid which comprises a promoter region capable of directing protein expression in an animal and/or human cells that is operably linked to a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582 of SEQ ID NO. 2.

II. (claims 14-18, 42-44) A transgenic animal having a genome comprising an alteration of the gene encoding LRP5 wherein the alteration is caused by the introduction of a nucleic acid for gene targeting by homologous recombination into embryonic stem cells or pluripotent cells comprising a first section homologous to mouse LRP5 gene and a second section homologous to another section of mouse LRP5 gene and between the first and second section a middle section comprising an engineered deletion of a portion of the LRP5 gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene.

III. (claims 19-20) A transgenic animal having a genome comprising an alteration of the gene encoding LRP6 wherein the alteration is caused by the introduction of a nucleic acid for gene targeting by homologous recombination into embryonic stem cells or pluripotent cells comprising a first section homologous to mouse LRP6 gene and a second section homologous to another section of mouse LRP6 gene and between the first and second section a middle section comprising an engineered deletion of a portion of the LRP6 gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene, wherein the transgenic animal has modulated Wnt activity, DKK activity, lipid levels or bone mass.

IV-VIII. (claims 21-29, 32-37) A method for studying bone mass development, a method for identifying surrogate markers of bone formation/resorption, a method for studying the effects of a test compound and the HBM gene on cardiac disorders, a method of screening of screening of cardio-protective treatments for bone mass modulation effects, or a method for identifying genes associated with bone mass, comprising the steps of:

a) providing a first group of animals

b) measuring at least one parameter of bone development in the animals

wherein the group of animals are selected from among:

IV. animals comprising a transgene for expressing LRP5,
V. animals comprising a transgene for expressing LRP6,
VI. animals in which the native LRP6 knocked out and HBM or another variant has been knocked into the LRP6 gene of the animals' genome,
VII. animals in which the native LRP5 is knocked out,
VIII. animals in which the native LRP6 is knocked out.

The method further comprises a step of administering a chemical compound and/or a surgical procedure to at least some of the animals prior to measuring at least one parameter of bone development in the animals.

IX. (claims 30, 31) A method for studying an effect of HBM on bone disorders comprising the steps of:

a) providing embryos of animals with a bone disorder phenotype,

b) introducing the nucleic acid of claim 1 and claim 4 into a first group of the embryos,

c) transferring the embryos to pseudopregnant mice;

d) measuring at least one paragmeter of development in the resulting mice.

X. (claims 38-41) A nucleic acid for gene targeting by homologous recombination comprising a first section homologous to mouse LRP5 gene and second section homologous to another section of mouse LRP5 gene, and between the first and second section, a middle section comprising an engineered deletion of a portion of the LRP5 gene, a nucleic acid sequence change, or a nucleic acid insertion, and wherein the nucleic acid is capable of homologous recombination with the endogenous gene.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 9, 2005.

Claims 1-13, drawn to a transgenic animal having somatic and/or germ cells comprising at least 15 contiguous nucleotide sequence of SEQ ID NO 2, including at least the thymine at position 582 of SEQ ID NO. 2, operatively linked to a promoter, are under consideration.

Information Disclosure Statement

The information disclosure statement filed January 16, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The IDS lists a reference by Courseaux et al. (sheet 1/3), and a reference by Schneider et al. (sheet 1/3). Neither of these references has been provided. If the references are to be considered, a copy of the publications must be provided.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-5, 7-13 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4, 6-8, 10, 12-15 of copending Application No. 10/477,238 (referred to as '238). This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-5, 7-13 of the instant application ('287) are the same as claims 1-4, 6-8, 10, 12-15 of ('238).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 5 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of copending Application No. 10/477,238. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 5 of the instant application ('287), drawn to a transgenic animal of claim 1, wherein the promoter region is a bone specific promoter region, encompasses claim 5 of '238, drawn to a transgenic animal of claim 1 wherein the promoter region is osteocalcin, osteopontin, and bone sialoprotein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3, 5, 7-12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-3, 5, 7-12 encompass transgenic humans. This is non-statutory matter. Amending the claims to recite "non-human animal" will be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence, SEQ ID NO. 2, encoding human High Bone Mass (HBM) protein, or a nucleic acid sequence comprising SEQ ID NO. 1, encoding human LRP5 operably linked to a ubiquitous promoter or a bone-specific promoter, stably integrated in its genome, wherein said mouse exhibits an increase in bone mass in more than one parameter selected from among bone density, bone strength, trabecular number, bone size, and bone tissue connectivity,

does not reasonably provide enablement for

a transgenic animal comprising a transgene construct comprising a nucleic acid sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582 of SEQ ID NO. 2 or SEQ ID NO. 1 operably linked to any promoter

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is to a transgenic animal comprising a transgene construct comprising a nucleic acid sequence encoding LRP5 operably linked to a bone specific promoter or a constitutive promoter, wherein the transgenic animal exhibits a bone phenotype comprising increased bone mineral density and to a transgenic animal comprising a transgene construct comprising a nucleic acid sequence encoding HBM operably linked to a bone specific promoter or a constitutive promoter, wherein the transgenic animal exhibits a bone phenotype comprising increased bone mineral density.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention broadly encompasses any transgenic animal. The specification at the time of filing teaches transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding HBM operably linked to a CMVβ actin promoter (specification, page 170, lines 20-21), transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding HBM operably linked to a type I collagen promoter (specification, page 170, lines 1-2), and transgenic mice comprising a nucleic acid sequence encoding LRP5, operably linked to a type I collagen promoter (specification, page 179, lines 1-3). While the specification teaches these transgenic mice, the specification does not enable an artisan to make and use any transgenic animal. At the time of filing, the art teaches that making transgenic overexpression animals is unpredictable. One reason for this unpredictability stems from the randomness in which the transgene integrates into the host's genome. Cameron (1997, Molecular Biotechnology, 7: 253-265) teaches, "a feature common to many transgenic experiments is the unpredictability transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene (Cameron, page 256, section 4 on transgene regulation and expression)." Thus, an artisan cannot predict where a transgene will integrate in the host genome, how many copies of a transgene will integrate into the host genome, what the transgene expression pattern is, of the resulting transgenic animal (with regards to how much transcript is produced by the cell and with regards to in which tissues express transgene, as enhancers from the host's genome may also influence transgene expression), and what the subsequent phenotype(s) is of the transgenic animal. As summarized by Mench (1999, Transgenic Animals in Agriculture, eds. Murray et al., CAB International: Oxon, pages 251-268), "because there can be so much variation in the sites of gene insertion, the numbers of gene copies transferred, and gene expression, every transgenic animal produced using microinjection is (theoretically, at least) unique in terms of its phenotype (Mench, page 259, bottom)." With regards to the instant invention, the phenotype observed in the transgenic mice is an increase in bone mass. The detectable increase in bone mass is dependent on the amount of transgene produced. In light of the teachings of Cameron and Mench, any transgenic animal comprising a transgene comprising SEQ ID NO. 1 or SEQ ID NO. 2, is not enabled for its full breadth of encompassing any transgenic animal comprising a transgene comprising SEQ ID NO. 1 or SEQ ID NO. 2 operably linked to a bone-specific promoter or a ubiquitous promoter, as an artisan would need to characterize each transgenic animal made and determine if whether enough copies of transgene had integrated into the genome, and if enough transgene is being expressed (as some transgene may insert near a repressor) such that a phenotype could be detectable. As such, in order for an artisan to predict all the possible phenotypes that result from making transgenic animals is undue experimentation. The specification as filed does not teach an artisan how to overcome the unpredictability associated with insertion of a transgene into the genome of an animal.

The claimed invention broadly encompasses any transgenic animal. This includes invertebrates. However, the specification at the time of filing does not teach an artisan how to use any transgenic invertebrate animal comprising a transgene construct comprising a bone specific promoter (see claims 5, 6, 8, 10, 11). No guidance was provided as to what tissue(s) a bone specific promoter would express in an invertebrate and no guidance was provided as to how to use a transgenic animal comprising a bone specific promoter. In order for an artisan to be enabled to use a bone specific promoter in an invertebrate is undue experimentation, as no guidance was provided as to where (if at all) a vertebrate bone specific promoter would express in an invertebrate.

The claimed invention broadly encompasses any transgenic animal comprising any promoter. However, at the time of filing, while the specification enables an artisan to use a ubiquitous promoter and a bone-specific promoter, the specification does not teach an artisan how to use any promoter such as a skin-specific promoter or a neural-specific promoter such that expression of SEQ ID NO. 2 or SEQ ID NO. 1 results in transgenic animals that have a bone phenotype. Alternatively, the specification does not teach that expression in skin or in the nervous system results in a detectable phenotype caused by the overexpression of SEQ ID NO. 2 or SEQ ID NO. 1. As the specification does not provide guidance as to how an artisan would make (i.e. identify and then use) transgenic animals comprising a skin-specific or neural-specific promoter, an artisan is not enabled for the full breadth of the scope of any promoter. It would be undue experimentation for an artisan to practice the claimed invention without guidance as to how to assay the biological effects of HBM or LRP5 in the skin or nervous system.

The claimed invention broadly encompasses a transgenic animal comprising a transgene comprising SEQ ID NO. 2 or SEQ ID NO. 4. However, at the time of filing, the art teaches that an artisan cannot predict whether expression of a heterologous protein will result in a transgenic animal exhibiting a predictable phenotype. Hammer, et al. (1990, Cell 63:1099-1112) demonstrated that transgenic mice that overexpressed human HLA-B27 and human β2-microglobulin (hβ2m) did not develop the human disease, spondyloarthropathies, whereas a rat that overexpressed human HLA-B27 and human β2-microglobulin (hβ2m) did (page 1099, second column, second paragraph). With regards to the instant invention, while the specification teaches transgenic mice comprising SEQ ID NO. 2 or SEQ ID NO.1, the specification does not teach how to overcome Hammer et al.'s teaching, such that an artisan can reliably make other transgenic animals, other than mice, that express SEQ ID NO. 2 or SEQ ID NO. 1 and exhibit a bone phenotype.

The claimed invention encompasses a nucleic acid sequence "comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582 of SEQ ID NO.2" (see claim 1). Claim 1 broadly encompasses any 15-mer comprising at least the thymine at position 582. Claim 1 thus encompasses any nucleic acid, including at least the thymine at position 582, read in any frame. This means that the peptides produced would encompass a peptide encoding part of HBM, and 2 other peptides which may not have any biological activity and/or which may have biological activity, but nothing in the art or the specification teaches how to detect such activity. While the specification teaches that the thymine at position 582 in SEQ ID NO. 2

corresponds to a glycine to a valine amino acid substitution (specification, page 92, lines 1-3), and expression of an LRP5 comprising the glycine substitution in transgenic mice results in mice with higher bone mass (e.g. specification, page 171, lines 10-16), the specification does not teach how to use any transgenic animals comprising any transgene comprising any 15-mer, comprising at least the thymine at position 582 of SEQ ID NO. 2, that can be read in any frame and produce a peptide with no activity. Similarly, the specification does not teach how to use any transgenic animals comprising any transgene comprising any 15-mer that can be read in any frame and produce any kind of activity. The specification, at the time of filing, teaches a specific reading frame and also teaches a specific phenotype that is detected in transgenic mice comprising the transgene. However, the claims as they read encompass other embodiments, of which neither the specification nor the art teach how to use in transgenic mice comprising such embodiments.

The claimed invention encompasses a sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 (claim 1) or SEQ ID NO. 1 (claim 4). This encompasses polynucleotides used as antisense. However, at the time of filing, the specification does not teach an artisan how to predictably obtain any 15-mer or longer polynucleotide and know that it would behave as antisense. At the time of filing, the use of DNA molecules such as antisense to predictably and routinely effect a biological change is not known in the art. For example, a review by Agrawal and Kanimalla (2000, Molecular Medicine Today, 61: 72-81) teaches that the use of antisense as a means of targeting a gene is unpredictable. "A good part of nucleotide design for its target RNA varies significantly, depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence. Introduction of oligonuclotides that contain certain sequence motifs, such as CpG and GGGG (hyper-structure-forming sequences) induce cell proliferation and immune responses.... If an antisense oligonuclotide possess self-complementarity or a palindromic sequence, it can form stable secondary structures such as short linear duplexes or hairpins. In such cases, secondary structure formation competes for binding to the target mRNA. In addition, these secondary structures can serve as decoys by binding to cellular factors, thereby inhibiting or inducing the functions of non-targeted genes, which could directly or indirectly alter the function of the gene being studied (page 77, second column, "Choice of oligonucleotide sequences," first and second paragraphs)." Thus, because not all antisense constructs will function as predicted, all antisense constructs need to be tested for function and efficacy. The specification does not provide any examples of antisense constructs that were able to reduce the expression level of a target gene and thus does not enable one skilled in the art to make and/or any antisense in a transgenic animal.

According to Merriam-Webster's online dictionary, "transgenic" means, "having chromosomes into which one or more heterologous genes have been incorporated either artificially or naturally." The use of the word "transgenic" raises two issues with regards to claims 12 and 13. First, the transgenic animals in claim 1 encompass animals that are not fertile (see claims 12 and 13), this means that there are some transgenic animals that cannot be continued as a line. This means that some transgenic animals comprising a certain genotype and phenotype are gone once the animal has died. In light of the teachings of Cameron (1997) and Mench (1999), the specification has not overcome the unpredictability of transgenesis and has not taught how to reliably generate another set of those transgenic animals which have died. In this respect, the specification does not enable the full breadth of claim 1, wherein the transgenic animals are infertile. Second, the transgenic animals in claim 1 encompass animals that do not pass the transgene on to its offspring (see claims 12 and 13). In light of the fact that "transgenic" means that the heterologous gene had been incorporated into the chromosome and that some of the transgenic animals in claims 12 and 13 are not passing on the transgene to its offspring suggests a contradiction in terms and suggests that the transgenic animals are not really transgenic.

The transgenic animals of claim 4 comprising a transgene construct comprising a nucleic acid sequence encoding LRP5 operably linked to a promoter exhibit a phenotype wherein bone mass is modulated. This means that the bone mass can increase or decrease relative to the non-transgenic animals. If this is the case, then while the specification teaches how to use transgenic animals wherein bone mass increases, the specification does not teach how to use transgenic animals wherein bone mass decreases. It would be undue experimentation for an artisan to use a transgenic animals wherein bone mass decreases because nothing in the specification teaches an artisan the relationship between overexpression of LRP5 and bone loss.

Therefore, while the specification, as filed, enables an artisan an artisan to make and use a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence, SEQ ID NO. 2, encoding High Bone Mass (HBM) protein or a nucleic acid sequence comprising SEQ ID NO. 1 operably linked to a ubiquitous promoter or a bone-specific promoter, stably integrated in its genome, wherein said mouse exhibits an increase in bone mass in more than one parameter selected from among bone density, bone strength, trabecular number, bone size, and bone tissue connectivity, the specification does not provide guidance commensurate for the full breadth of the claims for reasons described above.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

While the specification provides adequate written description transgenic mice comprising a transgene construct comprising SEQ ID NO. 2 and transgenic mice comprising a transgene construct comprising SEQ ID NO. 1, the specification fails to adequately describe other transgenic animals comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at position 582. Further, the specification does not provide adequate written description for any 15-mer or longer polynucleotide that is used as an antisense construct. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, while the Applicants have demonstrated a transgenic animal comprising SEQ ID NO. 2 or SEQ ID NO. 1, the Applicants have not taught the function of every 15-mer oligonucleotide up through the full length sequence of SEQ ID NO. 2, wherein any peptide encoded by any oligonucleotide of SEQ ID NO. 2 comprising at least the thymine at position 582 of SEQ ID NO. 2 has any activity. Further, the specification has not taught that all 15-mer and longer nucleotides behave as an antisense construct. The skilled artisan cannot envision all the possible variant nucleic acid sequences which would encode a peptide with a known structure and function and all possible variant nucleic acids which would function as antisense, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the full length SEQ ID NO. 2 and SEQ ID NO.1 meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that

Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al (U.S. Patent No. 6,770,461, filed April 5, 2000, patented August 3, 2004) in view of Watson et al. (1993, "The Introduction of Foreign Genes into Mice," *Molecular Biology of Watson Recombinant DNAs*, 2nd Edition, p 255-272).

Carulli et al. teach that the Zmax1 gene, has a role in bone formation. Carulli et al. teach that Zmax1 mRNA was primarily detected in areas of bone involved in remodeling, including the endosteum and trabecular bone within the metaphysis. Zmax mRNA was also detected in the periosteum, epiphysis, and in chondrocytes within the growth plate, particularly in the proliferating chondrocytes (Carulli et al., column 77, lines 16-25). The expression pattern of Zmax1 in the zone of proliferation and in osteoblasts and osteoclasts of the proximal metaphysic suggests that Zmax has a role in the process of bone growth and mineralization. The activity and differentiation of osteoblasts and osteoclasts are closely coordinated during development as bone if formed and during growth as well as in adult life as bone undergoes continuous remodeling (Carulli et al., column 78, lines 1-8). Carulli et al. teach that people who express the HBM gene, a mutant form of the Zmax1 gene, tend to have increased bone density and do not develop osteoporosis. In other words, the HBM gene is a suppressor of osteoporosis (Carulli et al., column 6, lines 16-25). While Carulli et al. teach that Zmax1 is expressed in bone and that people who express the mutant form of Zmax1, HBM, tend not to develop osteoporosis, Carulli et al. do not teach a transgenic animal comprising a transgene construct comprising a nucleic acid sequence encoding Zmax or HBM operably linked to a bone specific promoter or a constitutive promoter, wherein the transgene construct is stably integrated into the host animal's genome.

According to Watson, et al., "technical developments in recent years have provided mouse geneticists with a set of tools that they can use to perform in mice experiments previously restricted to lower organisms. They can now manipulate the genes of developing embryos and introduce foreign genes into embryos. Once these genes have integrated into the genome of the recipient embryo, the embryos or the adult animals that develop from them can be analyzed to determine the pattern of expression and the phenotypic effect of the introduced gene. This provides an opportunity not only to identify genetic elements that determine tissue-specific gene expression, but also to examine the phenotypic effects of the targeted expression of one gene or several genes acting in concert.... Transgenic mice can also provide model systems that can be used to broaden our understanding of human disease conditions (page 255, lines 5-18)." Watson et al. also describe the method used to generate transgenic mice. Watson et al. teach that pronuclear injection can be used to introduce a transgene construct that can be stably integrated into a mouse's genome (page 256, first column, second paragraph, lines 1-23).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence encoding Zmax1 or HBM operably linked to a constitutive promoter or a bone-specific promoter, wherein the transgene construct was stably integrated in the mouse's genome.

One having ordinary skill in the art would have been motivated to make a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence encoding Zmax1 or HBM operably linked to a constitutive promoter or a bone-specific promoter, wherein the transgene construct was stably integrated in the mouse's genome, in order to obtain a model system that can be used study the pathways involved in osteoporosis. Motivation was provided by Carulli et al. for teaching the relationship between bone and HBM and Zmax1.

There would have been a reasonable expectation of success given the results of Watson et al. for teaching how to make transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding Zmax1 or HBM operably linked to a constitutive promoter or a bone-specific promoter, wherein the transgene construct was stably integrated in the mouse's genome.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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